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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,010	12/14/2004	Ingemar Starke	056291-5188	4986

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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,010	STARKE ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21 are pending in the application.

Priority

1. Any non-provisional application claiming the benefit of one or more prior filed copending nonprovisional applications or international applications designating the United States of America must contain or be amended to contain in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications. Cross-references to other related application(s) may be made when appropriate.

"This application is a national stage entry under 35 U.S.C. § 371 of PCT/GB03/02499, filed June 10, 2003" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is the Wands factors, which are used to evaluate the enablement question. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman,

230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case, has claims which embrace 1,1-dioxo-2,3,4,5-tetrahydro-1,5-benzothiazepine compounds. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active in vivo. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrug will be suitable for the instant invention.

The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by claims 1-16 and 20-76. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

3. Claims 10-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In evaluating the enablement question, several factors are to be considered.

In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

HOW TO USE: Claims 12 and 13 are to a method of treating a disease, which is associated with the inhibition of IBAT. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The scope of the method claims are not adequately enabled solely based on inhibition of IBAT provided in the specification. Diseases and/or disorder(s) known to be associated with ileal bile acid transport (IBAT) inhibitory actîvity include atherosclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is difficult to treat many of the disorders claimed herein.

No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed 1,1-dioxo-2,3,4,5-tetrahydro-1,5-benzothiazepine compounds. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

The specification has no working examples on the use of the substituted 1,1-dioxo-2,3,4,5-tetrahydro-1,5-benzothiazepine, etc. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocyte, monocytes and/or macrophage infiltrate, intimital thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke, transient ischaemic attacks, etc..

4. Claims 15-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the pharmaceutical compositions of the compounds of formula I, does not reasonably provide enablement for the complex compositions of formula I as claimed herein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The pharmaceutical compositions and method of use of the instant invention where an additional active ingredient such as **HMG Co-A reductase inhibitors, bile acid binder, PPAR alpha and/or gamma agonist** is included in the compositions. The specification does not define that which is intended in the additional active ingredients, i.e. which HMG Co-A reductase inhibitors, bile acid binder, PPAR alpha and/or gamma agonist, etc.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 8-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claim 8 is vague and indefinite in that it is not known what is meant by the second occurrence of the species 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-mesylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine in lines 24-25 on page 40, which is a duplicate of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine in lines 21-23.

b) Claim 9 is vague and indefinite in that it is not known what is meant by "a compound of formula (I)" which is not present in independent claim 9.

c) Claims 10-12 are a substantial duplicate of claim 14 as the only difference is a statement of intended use, which is not given material weight. Note In re Tuominen 213 USPQ 89.

d) Claim 12 provides for the use of the compounds of formula (I), but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is

indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

e) Claims 12 and 13 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of ileal bile acid transport (IBAT). Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher

or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in cancer, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a

specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

f) Regarding claim 13, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claim 12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under

35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 11 of U.S. Patent No. 6,906,058. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds, compositions, process of preparing and method of use of the compounds of formula (I) embrace the compounds, compositions and method of use of the compounds of formula (I) of U.S. '058 where D is O.

8. Claim 20 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18 and 19 of copending Application No. 10/499,261. Although the conflicting claims are not identical,

they are not patentably distinct from each other because the complex composition of formula (I) which includes an additional active ingredient, i.e. PPAR alpha and/or gamma agonist.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claim 20 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18 and 19 of copending Application No. 10/499,379. Although the conflicting claims are not identical, they are not patentably distinct from each other because the complex composition of formula (I) which includes an additional active ingredient, i.e. PPAR alpha and/or gamma agonist.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 12-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 10/502,355. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions and method of use of the compounds of formula (I) as well as the complex composition of formula (I) which includes an additional active ingredient, i.e. HMG Co-A reductase inhibitor, bile acid binder, etc.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 10-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of copending Application No. 10/520,939. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions and method of use of the compounds of formula (I) as well as the complex composition of formula (I) which includes an additional active ingredient, i.e. PPAR alpha and/or gamma agonist, HMG Co-A reductase inhibitor, bile acid binder, etc.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claim 20 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23 and 24 of copending Application No. 10/499,893. Although the conflicting claims are not identical, they are not patentably distinct from each other because the complex composition of formula (I) which includes an additional active ingredient, i.e. PPAR alpha and/or gamma agonist.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of

copending Application No. 10/488,540. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds, compositions, process of preparing, complex compositions and method of use of the compounds of formula (I) are embraced by the compounds, compositions, process of preparing, complex compositions and method of use of the compounds of formula (I) of 10/488,540 where R^1 and R^2 are both C_{1-6}alkyl.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16, 20-69 and 73-76 of copending Application No. 10/451,262. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds, compositions, process of preparing, complex compositions and method of use of the compounds of formula (I) are embraced by the compounds, compositions, process of preparing, complex compositions and method of use of the compounds of formula (I) of 10/451,262 where R^3 and R^6 are both H; R^4 is MeS; R^5 is the compound of formula (IA) where D is O, R^7 is H; R^8 is H; A is hydrogen, hydroxyl or halo substituted phenyl; R^9 is H; m is 0; R^{11} is formula (IB) where R^{12} is H; p is 1; R^{13} is C_{1-4}alkyl; q is 0 or 1; X is -NHC(O)-; r is 0 or 1 and R^{15} is carboxy.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claims 10-21 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be in the alternative.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brenda Coleman

Brenda L. Coleman
Primary Examiner Art Unit 1624
September 27, 2005